Original Article

Perioperative change in neutrophil-to-lymphocyte ratio (NLR) is a prognostic factor in patients with completely resected primary pulmonary sarcomatoid carcinoma

Yong Won Seong, Sung Joon Han, Woohyun Jung, Jae Hyun Jeon, Sukki Cho, Sanghoon Jheon, Kwhanmien Kim

Department of Thoracic and Cardiovascular Surgery, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seoul, Korea

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Correspondence to: Kwhanmien Kim, MD, PhD. 82, Gumi-ro 173 Beon-gil, Bundang-gu, Seongnam-si, Gyeonggi-do 13620, USA.
Email: kmkim0070@gmail.com; kmkim0070@snubh.org.

Background: There has been controversy regarding prognostic factors for surgically resected primary pulmonary sarcomatoid carcinoma (PSC). Recently, several studies have shown that neutrophil-to-lymphocyte ratio (NLR) was a prognostic factor for various types of cancers from multiple organs. Therefore, we performed this study to evaluate whether NLR is related to prognosis after complete surgical resection of primary PSC.

Methods: From Oct. 2003 to Sep. 2015, a total of 50 patients underwent surgical resection for primary PSC. After excluding patients with any history of other malignancy and incompletely resected cases, a total of 37 patients were included, and data were retrospectively collected and analyzed. Change in postoperative NLR and the initial NLR (ΔNLR) was calculated from the perioperative complete blood count (CBC) results.

Results: Mean age of the cohort was 62.2±1.9 years, and 31 patients (83.8%) were male. Twenty patients (54.1%) were revealed as pN0. Overall 5-year survival rate was 50.3%. Seventeen patients (45.9%) had locoregional or distant metastases. Univariate survival analysis revealed age >70, ΔNLR >17 as risk factors for overall survival (P=0.009, 0.005) and disease-free survival (P=0.036, 0.018). Multivariate Cox-regression analysis revealed age >70 and ΔNLR >17 as independent risk factors for overall survival and ΔNLR >17 as the only independent risk factor for the disease-free survival.

Conclusions: In patients with completely resected primary PSC, perioperative ΔNLR had a significant effect on the overall survival and disease-free survival. Older age was also an independent risk factor for overall survival.

Keywords: Lung cancer; prognosis

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Introduction

Inflammation is known to increase the risk of many types of cancers (including bladder, cervical, gastric, intestinal, esophageal, ovarian, prostate and thyroid cancer) through oncogenic mutations, angiogenesis, and change in the tumor microenvironment (1). Neutrophils, as a key inflammatory cell type, are known to progress tumor by upregulating inducible NO synthase (iNOS) which results in increased release of reactive oxygen species that directly damages DNA. Neutrophils are also known to play an

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important role in tumor angiogenesis by expressing vascular endothelial growth factor (VEGF) and releasing matrix metalloproteinase-9 (MMP-9) which have been shown to have the most profound effects in mediating tumor angiogenesis (2). Many recent reports have revealed that serum neutrophil-to-lymphocyte ratio (NLR) is related to the prognosis of various type of cancers from multiple organs (3-13). Many studies have demonstrated a relationship between the initial preoperative NLR and prognosis in patients with various type of cancers including NSCLC, and some of the more recent studies demonstrated prognostic significance of postoperative NLR and change in NLR in gastric cancer and non-small cell lung cancer (NSCLC) as well, emphasizing the prognostic significance of the dynamic change in the NLR after the treatment (3-12).

Primary pulmonary sarcomatoid carcinoma (PSC) is a rare variety of tumors which is included in NSCLC category with its incidence reported to vary from 0.1% to 4.1% (14). Previous reports have shown poorer prognosis after surgical resection than other types of NSCLCs with prognostic factors such as complete resection, lymph node (LN) metastasis (14-18). Primary PSC is also known to be refractory to conventional chemotherapy and radiotherapy with higher possibility of earlier metastases (19). Therefore, we tried to investigate the effect of immunologic factor on this rare type of cancer. Because of its rare incidence, the actual prognosis and its risk factors of completely resected primary sarcomatoid carcinoma is not well known. We performed this study to evaluate if there is prognostic significance between perioperative change in NLR and survival in patients with completely resected primary PSC.

Methods

This study was approved by the Institutional Review Board of our institution (IRB Number: B-1809-495-111, Seoul National University Bundang Hospital). From October 2003 to September 2015, a total of 50 patients underwent surgical resection for primary PSC at our institution. After excluding incompletely resected cases, pM0 and patients who had any history of another type of cancer, a total of 37 patients were included in the analysis. Clinical and pathological data of the patients were retrospectively retrieved from our prospectively collected lung cancer database and from our electronic medical record system. The preoperative evaluation included a detailed clinical history of the patient and physical examination, complete blood count (CBC) and blood chemistry analysis, bronchoscopy, computed tomography (CT) scan of the chest and upper abdomen, positive-emission tomography (PET) scan of the whole torso, brain magnetic resonance imaging (MRI), and pulmonary function tests. If lymph nodal metastasis was suspicious from the imaging studies, transbronchial needle biopsy with an endobronchial ultrasound (EBUS) was performed. The histologic diagnosis of the primary sarcomatoid carcinoma was made according to the 8th edition of the American Joint Committee on Cancer (AJCC) staging system. Every patient underwent an anatomical resection (at least segmentectomy) of the cancer. Surgery of the patients was performed by thoracotomy or video-assisted thoracoscopic surgery (VATS) under general anesthesia. All the patients were regularly followed up at the outpatient department. The initial neutrophil-to-lymphocyte ratio (iNLR) was calculated from the CBC which was obtained within 1 week before the surgery, and the postoperative NLR (pNLR) was obtained from the immediate postoperative CBC. iNLR subtracted from pNLR (pNLR-iNLR) was defined as change in NLR (ΔNLR).

Statistical analysis

Statistical analysis was performed using the SPSS for Windows, version 20.0 (IBM Corporation, Armonk, NY, USA) and R 2.13.0 (The R foundation). Maximally selected chi-square test was used for estimating the cutoff point number. Chi-square test, Student's *t*-test, and log-rank test were used for the univariate analysis of the variables. Kaplan-Meier survival curve was used for estimating the overall survival and disease-free survival. Cox regression model was used for the multivariate analysis of the overall survival and disease-free survival.

Results

Patient characteristics and clinicopathologic results

The mean age of the overall cohort was 62.2±1.9 years. Thirty-one patients (83.8%) were male. The mean size of the primary tumor and mean maximum standardized uptake value (SUV) from PET-CT was 4.5±0.3 cm and 10.4±0.9, respectively. Twelve patients (32.4%) underwent surgery by VATS. Only one patient (2.7%) underwent segmentectomy, the others underwent lobectomy (75.7%), bilobectomy (10.8%), or pneumonectomy (10.8%). Five (13.5%) patients revealed to be stage pT1 and among

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these pT1 patients, there was no case of pT1a, but only pT1b and pT1c. Mean number of dissected LNs was 20.6±1.9, and 20 patients (54.1%), 9 patients (24.3%), and 7 patients (18.9%) were staged as pN0, pN1, and pN2 respectively. A total of 25 patients (67.5%) underwent adjuvant chemotherapy. Seven patients (18.9%) revealed mixed cell types, and 25 patients (67.6%) revealed pure sarcomatoid carcinoma. The preoperative and postoperative NLR for each case of the patients are depicted in *Figure 1*.

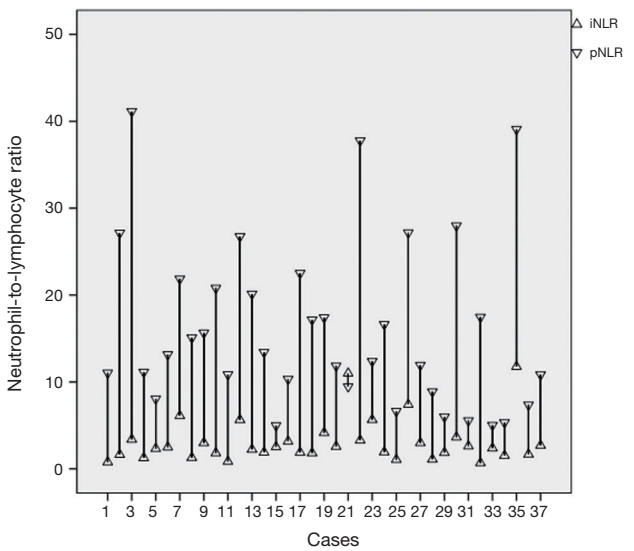

Figure 1 A line chart showing the change of iNLR and pNLR. This graph reveals the dynamic change of the value in each case of patients. iNLR, initial neutrophil-to-lymphocyte ratio; pNLR, postoperative neutrophil-to-lymphocyte ratio.

The mean value of the iNLR and ΔNLR were 3.1±0.4 and 13.0±1.4, respectively. Median follow-up duration was 4.62 years. During this follow-up period, a total of 17 patients (45.9%) had recurrences. Two patients (5.4%) had only locoregional recurrences, 8 patients (21.6%) had only distant recurrences, and 7 patients (18.9%) had locoregional and distant recurrences together. Among the 17 recurred patients, 7 patients (41.2%) recurred within 0.5 years after the surgical resection.

Analysis of the NLR

We used the receiver operating characteristics (ROC) curve to analyze the effect of the iNLR and ΔNLR on the overall survival and recurrence (*Figure 2*). The sensitivity and specificity of iNLR for overall survival were 50.0% and 60.0% with the area under the curve (AUC) 55.2%, and the sensitivity and specificity of ΔNLR for overall survival were 63.6% and 60.0% with the AUC 67.3%. The sensitivity and specificity of iNLR for recurrence were 58.8% and 60.0% with the AUC 55.2%, and the sensitivity and specificity of ΔNLR for recurrence were 64.7% and 60.0% with the AUC 64.4%, respectively. From these results showing the better profile of ΔNLR over iNLR, we decided to estimate the cutoff point of the ΔNLR for the overall survival. We performed the maximally selected chi-square test by downloading and using the maxstat package in R statistics which is freely downloadable (https://www.r-project.org), then the cutoff point of ΔNLR revealed to be 17 (20). We divided the 37 patients into two groups—the patients with ΔNLR ≤17 (n=27) and the patients with ΔNLR >17 (n=10).

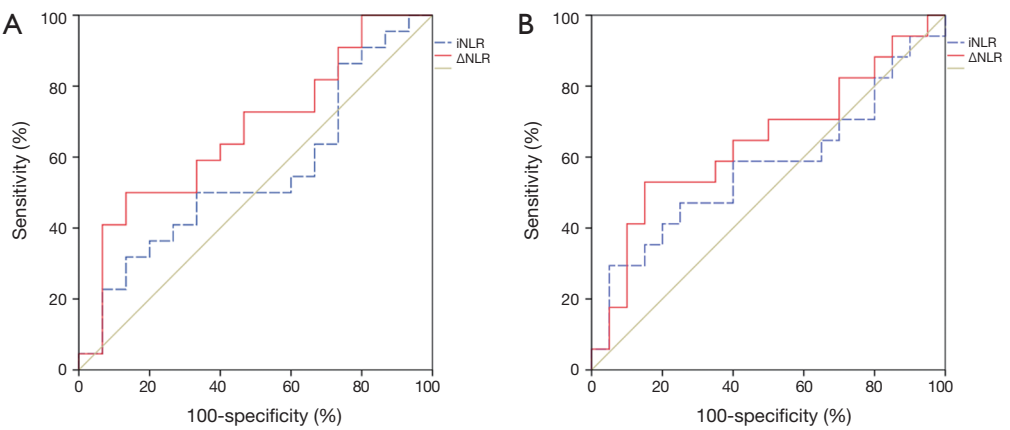

Figure 2 Analysis of the neutrophil-to-lymphocyte ratio (NLR) by the receiver operating characteristics (ROC) curve. (A) NLR & overall survival; (B) NLR and recurrence. iNLR, initial preoperative NLR; Δ NLR, change in NLR (postoperative NLR–iNLR).

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Table 1 Patient characteristics and clinicopathologic outcomes according to the change in neutrophil-to-lymphocyte ratio (NLR) cutoff value 17

Variables	ΔNLR ≤17 (n=27)	ΔNLR >17 (n=10)	P value
Age§	61.1±2.2	66.8±3.6	0.074
Male gender	22 (81.5%)	9 (90.0%)	1.000
Smoking			0.080
Never	5	4	
Former	8	2	
Current	14	4	
Diabetes	6	2	1.000
COPD	1	1	0.473
Cardiovascular disease	2	1	1.000
Neoadjuvant chemotherapy	3	2	0.597
Neoadjuvant radiation therapy	0	1	0.270
Preoperative FVC (%)§	97.3±3.3	99.8±5.5	0.702
Preoperative FEV1 (%)§	94.8±4.8	99.3±8.2	0.641
Preoperative DLCO (%)§	105.4±4.4	100.7±7.6	0.608
SUVmax of the mass§	10.6±1.2	9.9±1.0	0.739
Extent of the operation			0.681
Segmentectomy	1	0	
Lobectomy	21	7	
Bilobectomy	2	2	
Pneumonectomy	3	1	
No. of dissected LNs§	21.0±2.4	19.4±2.9	0.719
pT tumor size§	4.5±0.3	4.6±0.4	0.818
Visceral pleural invasion	12	5	1.000
Lymphatic invasion	12	5	1.000
Vascular invasion	12	3	0.481
pT stage			0.338
pT1	5	0	
pT2	11	7	
pT3	7	2	
pT4	4	1	
pN stage			0.749
pN0	14	6	
pN1	6	3	
pN2	6	1	
Postoperative complication			0.442
Air leak >5 days	3	3	
Pneumonia	1	0	
Arrhythmia	1	0	
Bleeding	0	0	
Adjuvant chemotherapy	17	8	0.445
Adjuvant radiation therapy	1	0	1.000

§, Student's *t*-test. ΔNLR, perioperative change in neutrophil-to-lymphocyte ratio; COPD, chronic obstructive pulmonary disease; FVC, forced vital capacity; FEV1, forced expiratory volume in one second; DLCO, diffusing capacity for carbon monoxide.

The 5-year overall survival rate was significantly poorer in the ΔNLR >17 group than in ΔNLR ≤17 group (10.0% *vs.* 66.1%, P=0.005). There was no significant difference in the patients' characteristics and the other clinicopathologic results between the two groups (*Table 1*).

Survival analysis

Median overall survival of the whole cohort was 5.69 years and the median disease-free survival was 3.15 years. The 5-year overall survival rate (5-YSR) and 5-year disease-free survival rate for the whole cohort was 50.3% and 45.2%, respectively. When comparing the two groups by ΔNLR, the group with ΔNLR >17 showed significantly poorer 5-year overall survival rate than the group with ΔNLR 17 or less (10.0% *vs.* 66.1%, P=0.005), and poorer 5-year disease survival as well (10.0% *vs.* 60.4%, P=0.018) (*Figure 3*).

Univariate analysis of the overall survival by the log-rank test revealed age more than 70 years (P=0.009) and ΔNLR >17 (P=0.005) to be the risk factors. Higher iNLR (2 or less *vs.* >2, P=0.794), higher pathologic T stage (pT1–2 *vs.* pT3–4, P=0.416), lymphatic invasion (P=0.509), vascular invasion (P=0.813), presence of LN metastasis (P=0.744),

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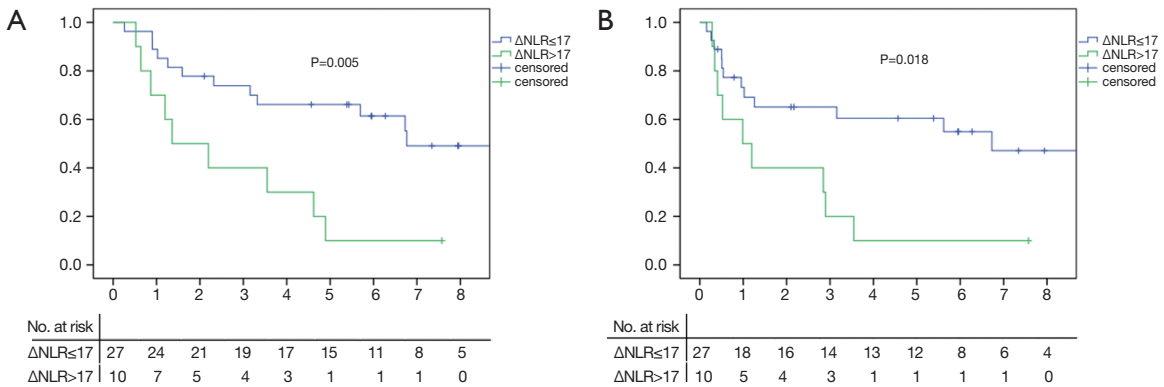

Figure 3 Overall survival (A) and disease-free survival (B) according to the change in neutrophil-to-lymphocyte ratio (Δ NLR).

and pure or mixed cell type (P=0.655) revealed no significant effect on overall survival. Neither neoadjuvant nor adjuvant chemotherapy had a significant effect on overall survival (P=0.442 and 0.662, respectively) as well. Age more than 70 years and ΔNLR >17 were also the risk factors for disease-free survival from the univariate analysis (P=0.036 and P=0.018 respectively). Multivariate Cox regression analysis revealed age >70 and ΔNLR >17 to be independent risk factors for the overall survival, and ΔNLR >17 to be the only independent risk factor for the disease-free survival (*Table 2*). This cut-off value 17 is just a value calculated only from our data which is not externally validated.

Discussion

Our data demonstrate the long-term clinical outcomes after complete resection of the pM0 primary PSC with the change in neutrophil-to-lymphocyte ratio as a significant prognostic factor. Fishback *et al.* reported in the year 1994 about 76 cases of pleomorphic sarcoma with a poor median survival of 0.83 years, but this study included who are not surgical candidates, and 12% of stage IV disease (21). Chang *et al.* reported a similar smaller series of 16 cases (7 underwent surgery) with a median survival of 0.25 years (22). Raveglia *et al.* reported in the year 2004 about 20 patients who all underwent surgical resection, and the patient all turned out to be pM0. The median overall survival was 0.67 years with early relapse of the disease, and the clinical outcomes seemed pessimistic even after surgery and adjuvant chemotherapy due to this early relapse (15). Park *et al.* reported in 2011 about outcomes after curative resection for sarcomatoid carcinoma of the lung with 5-YSR of 54.3%. In their series 43 patients (43.4%) had recurrence and 77.6% of the recurrences (33/43) were distant metastasis (23). Huang *et al.* reported in 2013 about 51 (37 patients underwent surgery) with a 5-YSR of 20.1%, and revealed tumor size and M stage as independent risk factors for prognosis (18). More recently, Okuda *et al.* reported in 2017 about 24 patients who had completely resected pM0 pulmonary pleomorphic carcinoma with 5-YSR of 54.7% and 5-year progression free survival 52.4%. They revealed vascular invasion and LN metastasis to be independent risk factors for overall survival (24). The survival data of our series is relatively favorable which is similar with those reported by Okuda *et al.*, and which is relatively higher than previous studies. These relatively better survival outcomes may be attributable to excluding patients with a history of other malignancy and only including completely resected pM0 patients. There were only five patients (13.5%) who were diagnosed as pT1, which might be due to the aggressive behavior of the tumor. Our data also revealed 45.9% (17/35) of recurrence and most of the recurrence was distant recurrence (15/17, 94.6%) with 41.2% (7/17) recurring within 0.5 years, which is similar with the report from Yuki *et al.* and Park *et al.* (16,23). There has been controversy regarding prognostic factors—some studies reported tumor size, some studies reported complete resection, and some studies reported LN metastasis (14,16,17,21,24,25). However, data from our series revealed no significant relationship between prognosis and tumor size, pT stage, tumor composition (pure or mixed sarcomatoid), LN metastasis. Adjuvant chemotherapy had no prognostic significance on survival from our series, similar to reports from Lin *et al.* and Raveglia *et al.* (14,15).

Regarding the NLR, activated neutrophils can release matrix metalloproteinases (MMPs), especially MMP-9,

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Table 2 Overall survival and disease-free survival analysis

Variables	Univariate analysis§	Multivariate analysis†		
	P value	P value	HR	95% CI
Overall survival				
Age >70 years	0.036	0.020	3.916	1.245–12.32
pT1-2 *vs.* pT3-4	0.416	0.061	0.344	0.113–1.048
Lymphatic invasion	0.509			
Vascular invasion	0.813			
Neoadjuvant chemotherapy	0.442			
Lymph node metastasis	0.744	0.474	1.607	0.622–4.152
Adjuvant chemotherapy	0.662			
ΔNLR >17	0.005	0.035	2.970	1.079–8.179
Disease-free survival				
Age >70 years	0.009			
pT1-2 *vs.* pT3-4	0.416			
Lymphatic invasion	0.625			
Vascular invasion	0.912			
Neoadjuvant chemotherapy	0.442			
Lymph node metastasis	0.905			
Adjuvant chemotherapy	0.662			
ΔNLR >17	0.018	0.014	3.087	1.260–7.561

§, log-rank test; †, Cox regression analysis. HR, hazard ratio; CI, confidence interval; ΔNLR, perioperative change in neutrophil-to-lymphocyte ratio.

which activates potent angiogenic factors (VEGF, fibroblast growth factor-2). On the other hand, lymphocytes act as a suppressor of cancer progression. Cytotoxic lymphocytes can kill tumor cells and are applicable for cancer immunotherapy (12). Tsubata *et al.* reported that VEGF expression was present in many cases of pulmonary pleomorphic carcinoma and a higher score of angiogenesis was significantly related to a poorer prognosis (26). The NLR is a readily available, inexpensive, and can be easily calculated and obtained from the database compared to other molecular markers. Earlier reports about NLR mostly focused on the significance of the initial (pretreatment) NLR. Khunger and colleagues reported the clinical significance of post-treatment NLR in 109 patients with NSCLC treated with nivolumab, which revealed that higher post-treatment NLR was related with poorer survival and non-respondence to the treatment (27). However, some of the recent papers are more focusing on the clinical significance of the change in NLR. Dan *et al.* reported the postoperative NLR change was an independent prognostic factor for patients undergoing radiofrequency ablation for small-sized hepatocellular carcinoma (28). Min *et al.* and Li *et al.* reported similar results for gastric cancer and colon cancer, respectively (12,29). Our data also revealed similar results, with ΔNLR being the independent prognostic factor for the overall survival and disease-free survival. We carefully suspect that more dynamically increased NLR after the surgery reflects higher neutrophil activity over lymphocyte activity after the surgery, which resulted in poorer survival. We measured postoperative NLR from immediate postoperative laboratory data to minimize the effect of postoperative infection or physical invasiveness from the surgery.

This study is a retrospective study with a small number

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of patients which can be the limitation. Further multicenter prospective study with a larger number of patients should be needed.

In conclusion, ΔNLR was significantly associated with poorer overall survival and disease-free survival in the patients with completely resected primary PSC and had better statistical significance than the initial preoperative NLR. The prognosis was poor in patients with higher ΔNLR, with the 5-year survival rate of 10.0% and the 5-year disease-free survival rate of 10.0%. More careful follow-up plan might be considered for patients with higher ΔNLR.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study was approved by the Institutional Review Board of our institution (IRB Number: B-1809-495-111, Seoul National University Bundang Hospital).

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